

Application No. 09/933,680

Amendment Dated 7/15/2003

Reply to Notice of Non-Compliant Amendment Dated June 10, 2002

### **REMARKS/ARGUMENTS**

By this Amendment, claims 7-9 and 13 are canceled (claims 15-25 were previously canceled by Preliminary Amendment), claims 1, 10, 12, and 14 are amended, and claims 26-34 are added. Claims 1-6, 10-12, 14, and 26-34 are pending.

This Amendment is compliant with the voluntary revised amendment practice in that a complete listing of all claims is provided with the claims in ascending numerical order.

The Examiner's courtesy in granting an interview to Applicants' representative on June 25, 2003 is gratefully acknowledged. Amendments additional to those presented in the non-compliant Amendment are made in light of the interview to more fully claim the full scope of the invention.

New claims 27, 29 and 30 correspond to original claims 16, 18 and 19, which were canceled by prior attorneys for Applicant. The claims are identified herein as "New" rather than "Reinstated-formerly claim #" because of minor differences, including claim dependencies. In claim 27, a change has been made to correct the antecedent basis for "the bi-functional carbohydrate-protein linking agent."

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

#### **Claim Rejections – 35 USC § 102**

The Examiner rejects claims 1-4, 7, 9, 12, and 14 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,891,196 and claims 1-4, 7, 9-12, and 14 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,378,224. These rejections are respectfully traversed.

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None of the applied references, taken alone or in combination, disclose or suggest the claimed invention, a method of treating an implantable biological tissue, wherein said method comprises (1) stabilizing glycosaminoglycans on the tissue and (2) cross-linking proteins on the tissue, wherein the stabilization of glycosaminoglycans on the tissue comprises contacting the tissue with (a) a water-soluble carbodiimide composition having a pH of 6.9 to 7.9, (b) a carbohydrate oxidizing agent, or (c) a heterofunctional azide reagent, provided that when the stabilizing comprises contacting the tissue with the water-soluble carbodiimide composition, the cross-linking comprises contacting the tissue with glutaraldehyde.

The '196 patent discloses a method of treating a tissue for implantation comprising (a) treating the tissue with a crosslinking agent such as glutaraldehyde, (b) treating the tissue with carboxyl activating compounds such as carbodiimides (e.g., EDC, DCC, EAC)), (c) contacting the tissue with a polyamine compound, and (d) contacting the tissue with heparin. Steps (b)-(d) were performed at pH 5.0.

The '224 patent discloses a method of treating a tissue for implantation comprising treating the tissue with glutaraldehyde, treating the tissue with water soluble carbodiimide at pH 5.0, and treating the tissue with a calcification inhibitor. Treating the tissue with a bridging agent such as aliphatic diamine, hexanediamine, is also disclosed.

Accordingly, reconsideration and withdrawal of the Section 102 rejections of claims 1-4, 7, 9-12, and 14 are respectfully requested.

Claim Rejections – 35 USC § 103

Claims 5 and 6 have been rejected as being obvious under 35 U.S.C. 103(a) over U.S.

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Patent No. 5,891,196 and U.S. Patent No. 4,378,224 and further in view of U.S. Patent No. 5,447,536. This rejection is respectfully traversed.

The rejection over the '196 patent is obviated by the present amendment of claim 1, from which claims 5 and 6 depend.

Further, claims 5 and 6 have been rejected over a combination of the '224 patent and the '536 patent. However, the Examiner fails to show that one of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the reference teachings to reach the invention. Such motivation is not present in either of the applied references. In particular, the '536 patent does not provide a suggestion or motivation for stabilizing of glycosaminoglycans on the tissue with (a) a water-soluble carbodiimide composition having a pH of 6.9 to 7.9, (b) a carbohydrate oxidizing agent, or (c) a heterofunctional azide reagent, provided that when the stabilizing comprises contacting the tissue with the water-soluble carbodiimide composition, the cross-linking comprises contacting the tissue with glutaraldehyde.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Regarding the pH, the '536 patent cannot be relied upon to disclose that the pH of a stabilizing reaction can be in a range from 6.9 to 7.4 because it does not teach stabilizing glycosaminoglycans (GAGs) on the tissue. Moreover, the '536 patent does not teach stabilizing glycosaminoglycans when using (i) the water-soluble carbodiimide composition at pH of 6.9 to

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7.9 and (ii) glutaraldehyde (as a cross-linking agent). The '536 patent specifically teaches cross-linking the tissue proteins in the absence of glutaraldehyde. The '536 patent does not disclose any particular advantages in using pH from about 6.5 to 7.4. Consequently, one skilled in the art would not have been motivated to combine teachings of the '536 patent with the '196 patent and/or '224 patent for stabilizing GAGs using the water-soluble carbodiimide at pH range from 6.9 to 7.4 and cross-linking with glutaraldehyde.

Accordingly, reconsideration and withdrawal of the Section 103 rejection are respectfully requested.

In addition, the attached Rule 132 Declaration of Narendra Vyavahare, Ph.D., describes prior unappreciated properties of the above stabilizing agents used by the claimed methods of the invention. Specifically, prior to the present invention, nobody appreciated the undesirable effect of low pH on collagen and other tissue proteins and that using carbodiimide and glutaraldehyde at pH of about 5 (acidic range), which is an optimal range for carbodiimide's reactivity, will cause excessive cross-linking of glycosaminoglycans (GAGs) and thereby a loss of flexibility of a cross-linked implant. The inventors, were first to recognize that stabilizing GAGs on a tissue by using carbodiimide at a pH of 6.9 to 7.9 (which is not the optimal range for reactivity purposes) and cross-linking with glutaraldehyde yield a more flexible attachment of GAGs to the implant. Such prior unappreciated properties are further evidence of the non-obviousness of the invention.

Claims 26-31 and 34

Regarding claims 26-31 and 34 (formerly claims 15-21), Applicants reinstate these

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claims with minor changes reflecting the proper claim numbering and corrected antecedent basis (claim 27), for they were inadvertently canceled by previous attorneys in the Preliminary Amendment of August 22, 2001. As discussed at the interview, claims 15-21 were never restricted by the Office Action of June 6, 2001 in parent application Serial No. 09/558,709. Even though there was a species election requirement in the parent application with respect to claims 7-13, and 14-19, it is respectfully submitted that claims 26-30 (formerly claims 15-19) should now be examined for at least the same reasons that claim 14 has been examined together with the claims of Group I.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,  
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